

EDITORIAL COMMENT

Prognostic Value of Electrophysiologic Studies in Brugada Syndrome*

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A decade has passed since Pedro and Joseph Brugada (1) discovered an electrocardiographic (ECG) marker for sudden cardiac death in a subset of patients with idiopathic ventricular fibrillation (VF) characterized by ST-segment elevation in the right precordial leads (V_1 to V_3) with a right bundle branch block pattern. This clinical entity, quickly recognized as the Brugada syndrome, has drawn widespread attention from cardiologists, electrophysiologists and arrhythmia scholars throughout the world. We have now learned that the Brugada syndrome is a familial disease with an autosomal dominant transmission with incomplete penetrance (2). In addition, the genetic cause of the syndrome has been identified as a mutation in the cardiac sodium channel gene, *SCN5A* (3).

The clinical presentation of the Brugada syndrome is nocturnal sudden death due to VF occurring mostly in men. The syndrome is endemic in Southeast Asia and Japan, where it is also known as sudden unexplained death syndrome, and the incidence has been estimated to range between 5 and 66 events per 100,000 people (2,4). However, the true incidence may yet to be realized as more physicians become cognizant of the ECG pattern associated with the Brugada syndrome and hence, diagnose more cases.

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It is well known that this ECG pattern can wax and wane and may be unmasked by sodium channel blockers (5). However, there are a number of conditions with a similar ECG pattern similar to that of the Brugada syndrome that must be considered (6). In other words, not all patients with the Brugada ECG pattern will have the same high risk of sudden cardiac death (SCD). More importantly, the increase in the number of asymptomatic patients with the Brugada ECG pattern poses a therapeutic dilemma to physicians. While treatment of symptomatic cases has been studied, there have been, unfortunately, little data to guide the management of asymptomatic patients.

In this issue of the *Journal*, Kanda et al. (7) confirm

previous reports that symptomatic patients (aborted SCD or syncope) are at an inordinate risk of SCD (4,8,9). Of the 34 patients in their study, 15 patients (44%) either died suddenly or developed VF during the follow-up period (mean of 38 months). Their observation is similar to that of a recent article by Brugada et al. (9) showing that 44 of 71 patients (62%) with a history of aborted SCD and 14 of 73 patients (19%) with a history of syncope developed either SCD or documented VF in the ensuing months (mean follow-up period of 54 and 26 months, respectively).

When compared to the Brugada et al. (9) findings, the event rates described by Kanda et al. (7) are slightly lower in the aborted SCD population but higher in the syncope population. The small differences in event rates between the two studies can probably be explained by the longer follow-up time for the aborted SCD group and shorter follow-up period for the syncope group in the Brugada et al. (9) study.

While these two studies are similar in term of the prognosis of symptomatic patients, they differ with respect to the prognostic values of the inducibility of sustained ventricular arrhythmia. The Kanda et al. (7) data suggest that inducibility of ventricular arrhythmia had no prognostic value in predicting long-term outcomes because many of their patients with noninducible, sustained ventricular tachycardia (VT) developed either SCD or VF. In contrast, Brugada et al. (9) found that the only variable with predictive value for SCD or VF was the inducibility of ventricular arrhythmias during electrophysiological studies. Examining the differences between the two studies, one realizes that Brugada et al. (9) have a much larger sample size. However, Brugada et al. (9) relied on registry information from multiple institutions throughout the world compared to the single institution and somewhat homogeneous population from Japan described by Kanda et al. (7).

The number of patients with inducible, sustained ventricular arrhythmias in the Kanda et al. (7) study is slightly lower than seen by Brugada et al. (9). However, many of the so-called noninducible patients in the Kanda et al. (7) study had inducible, nonsustained VT. Whether or not nonsustained VT has any prognostic value remains unclear. However, if one incorporated nonsustained VT as a positive electrophysiologic study, Kanda et al. (7) probably would not be able to conclude that inducibility of ventricular arrhythmias is not helpful in predicting long-term outcome because there would be only four patients in their study with no inducible ventricular arrhythmias.

Although it is not possible to easily reconcile the differences between these two studies, both data form a consensus that symptomatic patients with the Brugada ECG pattern are at very high risk of SCD and should be treated with implantable cardioverter defibrillators (ICDs). The challenge is how to treat asymptomatic patients? Should electrophysiologic studies be done to screen for high risk patients?

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Management of asymptomatic patients becomes a critical issue because the incidence of asymptomatic Brugada syndrome is relatively high, especially in Japan and Asia. For example, Miyasaka et al. (10) reported that a substantial number of citizens in the city of Moriguchi, Japan had the Brugada ECG pattern. The Brugada ECG pattern was found in 98 of 13,929 of patients and was astonishingly high (2.14%) in the male subjects. But Miyasaka et al. (10) found no difference in mortality rate between patients with and without the Brugada pattern. This is in sharp contrast to the Brugada et al. (9) finding that 16 of 190 (8%) asymptomatic patients with Brugada-type ECG patterns had either SCD or VF during the two-year follow-up period. Again, it is difficult to compare the two studies because the population of Moriguchi studied by Miyasaka et al. (10) were older (58 ± 10 years) than the asymptomatic patients in the Brugada et al. (9) study (40 ± 16 years). More importantly, subjects younger than 40 years with no structural heart disease were excluded from the Miyasaka et al. (10) study because no ECG examination was available. Therefore, the authors may have overlooked any high risk patients younger than 40 years. It is also noteworthy that many of the patients with sudden unexplained death syndrome or Brugada syndrome tend to be younger than 40 years. Thus, the older population with a greater female distribution studied by Miyasaka et al. (10) excluded the high-risk young male population and resulted in an overall better prognosis.

Nevertheless, it is clear that the asymptomatic patients have a much lower risk of sudden cardiac death than symptomatic patients. The dilemma is that there are many more asymptomatic patients than symptomatic patients—and since the ICD is highly effective in preventing death among symptomatic patients many lives could be potentially saved by ICD if we could identify the high risk, asymptomatic patients as well.

Brugada et al. (9) recommended ICD treatment for asymptomatic patients whose sustained ventricular arrhythmias could be induced and no ICD treatment for those without inducible ventricular arrhythmias. This is based on their finding that 6 of 35 patients (17%) with inducible ventricular tachyarrhythmias had an arrhythmic event compared to only 1 of 45 patients (2%) with non-inducible sustained VT. At present, these are the only data available to guide our treatment approach for asymptomatic patients with the Brugada-type ECG pattern. Unfortunately, data from the Kanda et al. (7) study are not relevant to asymptomatic patients because they included only symptomatic patients with aborted SCD or syncope. Further study with larger populations aiming to determine the value of VT induction in risk stratification needs to be carried out.

What should the role of electrophysiologic studies be in patients with Brugada syndrome? For the symptomatic patients (aborted SCD or syncope), ICD implantation without electrophysiologic studies is appropriate. It is my

personal preference that it is best to implant a dual-chamber ICD rather than a single-chamber ICD because atrial tachyarrhythmias, especially atrial fibrillation and bradycardia, are not infrequent in this population (2). Asymptomatic patients, however, should undergo electrophysiologic studies and if inducible, then ICD implantation is appropriate. Noninducible patients should be followed up regularly and if they become symptomatic, then ICD treatment is appropriate. Additionally, since the Brugada population, especially in Asia, often has nocturnal VF during sleep, a home automatic external defibrillator should be considered for noninducible asymptomatic patients.

Clearly more study is needed to shape our therapeutic approaches for patients with Brugada syndrome. As more data become available, the preceding guideline may have to be modified and improved. Meanwhile, electrophysiologic studies to determine inducibility of sustained ventricular arrhythmias remain an important part of risk stratification for the asymptomatic patient with Brugada syndrome.

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